In the Specification

Please replace the second paragraph on page 1 as amended as follows:

Technical Field

~~The present invention~~ This disclosure relates to therapeutic or prophylactic agents for preventing nausea and vomiting. Particularly, ~~the present invention~~ this disclosure relates to therapeutic or prophylactic agents for preventing nausea and vomiting caused by μ-opioid agonists represented by morphine.

Please replace the paragraph spanning pages 3 and 4 as follows:

Compounds ~~according to the present invention~~ are already disclosed for the following uses: improvement effects against dependence and tolerance to opioids (U.S. Pat. No. 5,352,860); immunomodulation, immunosuppression, and rheumatoid therapeutic uses (PCT Publication Nos. WO 95/13071, WO 91/07966, and WO 95/17189); cocaine dependence treatment (U.S. Pat. No. 5,411,965); and antitussive uses (PCT Publication No. WO 94/14445). However, these reports do not suggest anything about the therapeutic or prophylactic effects against nausea and vomiting~~, as represented by the present invention~~.

Please replace the first full paragraph on page 4 as follows:

Oxymorphone quaternary salt compounds in Japanese Unexamined Patent Application Publication No. 1-68376 and N-methylnalorphine in PCT Publication No. WO 01/13909 are reported as morphinan derivatives showing anti-emetic effects. However, the therapeutic or prophylactic effects against nausea and vomiting of indolomorphinan derivatives, quinolinomorphinan derivatives, and 7-benzylidenemorphinan derivatives ~~according to the present invention~~ cannot be anticipated from these reports.

Please replace the paragraph spanning pages 4 and 5 as amended as follows:

~~Summary of the Invention~~

~~The invention provides~~ It could therefore be advantageous to provide a therapeutic or prophylactic agent which can be widely used for preventing nausea and vomiting due to an emetic drug administration. In particular, ~~the invention provides~~ it could be advantageous to provide a therapeutic or prophylactic agent for preventing nausea and vomiting due to μ-agonists represented by morphine.

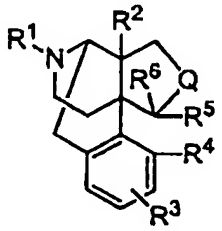
Please replace the first full paragraph on page 5 as follows:

Summary

~~With the aim of resolving the aforementioned circumstances, the inventors of the present invention have~~ We conducted intensive studies and found that a compound group consisting of particular morphinan derivatives exhibits anti-emetic activity while the side effects are mild and they barely decrease the analgesic effects of morphine.

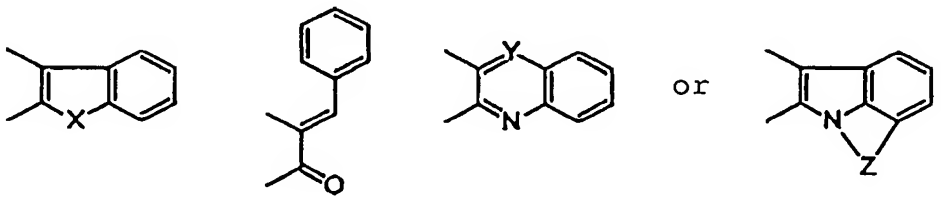
Please replace the paragraph spanning pages 5, 6, 7 and 8 as follows:

~~The present invention provides~~ We provide that a morphinan compound represented by general formula (I):



can be used as a therapeutic or prophylactic agent for preventing nausea and vomiting, [where R^1 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aryl group having 6 to 12 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having

3 to 7 carbon atoms, a furanylalkyl group (where the alkyl moiety has 1 to 5 carbon atoms), or a thiophenylalkyl group (where the alkyl moiety has 1 to 5 carbon atoms); R^2 and R^3 are mutually independent and represent a hydrogen atom, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, an alkenyloxy group having 3 to 5 carbon atoms, an aralkyloxy group having 7 to 16 carbon atoms, an arylalkenyloxy group having 7 to 16 carbon atoms, an alkanoyloxy group having 2 to 6 carbon atoms, an alkenoyloxy group having 4 to 6 carbon atoms, an arylalkanoyloxy group having 7 to 16 carbon atoms, or an alkyloxyalkoxy group having 2 to 10 carbon atoms; R^4 and R^5 together form an --O--, --S--, or --CH_2-- bond, or are mutually independent and R^4 represents a hydrogen atom, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 2 to 6 carbon atoms and R^5 represents a hydrogen atom; R^6 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, an arylalkyl group having 7 to 16 carbon atoms, an arylalkenyl group having 7 to 16 carbon atoms, a hydroxyalkyl group having 1 to 5 carbon atoms, an alkoxyalkyl group having 2 to 12 carbon atoms, a COOH-- group, or an alkoxycarbonyl group having 2 to 6 carbon atoms; and -Q- moiety represents a group as follows:



(where these structures may have one or more substituents selected from the group consisting of a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a nitro group, an alkyl group having 1 to 5 carbon atoms, a hydroxyl group, an oxo group, an alkoxy group having 1 to 5 carbon atoms, a trifluoromethyl group, a trifluoromethoxy group, a cyano group, a phenyl group, a hydroxyalkyl group having 1 to 5 carbon atoms, an isothiocyanato group, SR^8, SOR^8, $SOOR^8$, $(CH_2)_rOR^8$,

$(CH_2)_rCOOR^8$, $SOONR^9R^{10}$, $CONR^9R^{10}$, $(CH_2)_rNR^9R^{10}$, and $(CH_{.2})_rN(R^9)COR^{10}$ (where r is an integer from 0 to 5, R^8 represents an alkyl group having 1 to 5 carbon atoms, R^9 and R^{10} are mutually independent and represent a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, or a cycloalkylalkyl group having 4 to 7 carbon atoms), and where X represents an oxygen atom, a sulfur atom, a CH=CH, or NR^7 group (where R^7 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, an arylcarbonyl group having 7 to 13 carbon atoms, an alkylsulfonyl group having 1 to 5 carbon atoms, an arylsulfonyl group having 6 to 12 carbon atoms, an aralkylsulfonyl group having 7 to 13 carbon atoms, an aralkyl group having 7 to 16 carbon atoms, an arylalkenyl group having 7 to 16 carbon atoms, an alkanoyl group having 2 to 6 carbon atoms); Y represents a nitrogen atom or a CH group; and Z represents a bridge bond having 2 to 5 carbon atoms (where one or more carbon atoms may be replaced with a nitrogen, oxygen, or sulfur atom, and an aromatic or heteroaromatic ring having 5 to 12 carbon atoms or a cycloalkyl ring having 5 to 9 carbon atoms may be fused so as to share 2 or 3 skeletal carbon atoms)].

Please replace the paragraph spanning pages 8 and 9 as amended as follows:

Detailed Description

~~In embodiments according to the present invention, compounds~~ Compounds represented by General Formula (I) are preferably used. In particular, preferable substituents of the compounds represented by General Formula (I) are as follows:

Please replace the paragraph spanning pages 11 and 12 as follows:

Preferably, the substituent of the organic group is a fused benzene, fused pyridine, fused cyclohexane, or fused cyclopentane ring, a fluorine, chlorine, bromine, or iodine atom, a nitro group, an alkyl group having 1 to 5 carbon atoms, a hydroxyl or oxo group, an alkoxy group having 1 to 5 carbon atoms, a trifluoromethyl, trifluoromethoxy, cyano, or phenyl group, a hydroxyalkyl group

having 1 to 5 carbon atoms, an isothiocyanato group, an SR^8, SOR^8, $SOOR^8$, $(CH_2)_rOR^8$, $(CH_2)_rCOOR^8$, $SOONR^9R^{10}$, $CONR^9R^{10}$, $(CH_2)_rNR^9R^{10}$, or $(CH_2)_rN(R^9)COR^{10}$ group (where r is an integer from 0 to 5, R^8 represents an alkyl group having 1 to 5 carbon atoms, R^9 and R^{10} are mutually independent and represent a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, or a cycloalkylalkyl group having 4 to 7 carbon atoms). Specifically, a fused benzene, fused cyclohexane, or fused cyclopentane ring, a fluorine, chlorine, bromine, or iodine atom, a nitro, methyl, ethyl, isopropyl, hydroxy, oxo, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, cyano, phenyl, hydroxymethyl, hydroxyethyl, isothiocyanato, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, methoxymethyl, ethoxymethyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, sulfamoyl, dimethylsulfamoyl, dimethylcarbamoyl, dimethylamino, dimethylaminomethyl, or amino group is preferable. An unsubstituted organic group is also preferably included ~~in the present invention~~. However, the ~~present invention~~ disclosure is not limited to these substituents.

Please replace the paragraph spanning pages 12 and 13 as follows:

Examples of pharmacologically preferable acid addition salts include inorganic salts such as hydrochloride, sulfate, nitrate, hydrobromate, hydroiodate, and phosphate; organic carboxylate salts such as acetate, lactate, citrate, oxalate, glutarate, malate, tartrate, fumarate, mandelate, maleate, benzoate, and phthalate; and organic sulfonate salts such as methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and camphorsulfonate. Among them, hydrochloride, hydrobromate, phosphate, tartrate, methanesulfonate are most preferable, but ~~the present invention is~~ we are not limited to these salts.

Please replace the first full paragraph on page 13 as follows:

Compounds represented by General Formula (I) ~~of the present invention~~ can be prepared by

processes described in, for example, PCT Publication Nos. WO 94/14445, WO 97/11948, WO 89/00995, and WO 95/31463, and Heterocycles, 45, 2109, (1997).

Please replace the paragraph spanning pages 13 and 14 as follows:

The compounds represented by General Formula (I) ~~according to the present invention~~ are useful for controlling vomiting due to radiotherapy for cancer, a toxic agent, a toxin, metabolic disorder (for example, gastritis), hyperemesis, rotatory vertigo, kinetosis (for example, carsickness), postoperative sequelae, gastrointestinal dysfunction, gastrointestinal hypokinesia, visceral pain (for example, myocardial infarction and peritonitis), migraine, an increase in intra-cranial pressure, and a decrease in intra-cranial pressure such as altitude sickness. The term "vomiting" includes nausea, emesis, and vomiting. Vomiting includes acute vomiting, delayed vomiting, and premonitory vomiting.

Please replace the paragraph spanning pages 14 and 15 as follows:

Specifically, the compounds represented by General Formula (I) ~~according to the present invention~~ are significantly useful for controlling vomiting due to the following emetic drugs:

(1) Anticancer drugs (antineoplastic agents): For example, cyclophosphamide, carmustine, lomustine, chlorambucil, busulfan, melfalan, mecloretamine, vinca alkaloids (e.g., etoposide, vinblastine, vincristine, etc.), ergot alkaloids (e.g., ergot alkaloid, bromocriptine, etc.), fumagillin derivatives (e.g., (3R,4S,5S,6R)-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxirany- l]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate), methotrexate, emethine, mustine, cysplatine, dacarbazine, procarbazine, dactinomycin, doxorubicin, mytomycin C, bleomycin, asparaginase, daunorubicin, floxuridine, cytarabine, fluorouracil, mercaptopurine, mitotane, procarbazine, streptozocin, tamoxifen, thioguanine, and busulfan.

(2) Antibiotics: For example, erythromycin and its derivatives [e.g., erythromycin such as

erythromycin A, B, C, and D and their derivatives (e.g., N-demethyl-N-isopropyl-8,9-anhydroerythromycin A-6,9-hemiacetal), clarithromycin], aminoglycoside (e.g., streptomycin, neomycin, gentamicin), actinomycin, adriamycin, and cycloheximide.

(3) Morphine, its derivatives, and its salts [e.g., opioid analgesics such as morphine and its salts, therapeutic drugs for male erectile dysfunction (impotence) such as apomorphine and its salts, and therapeutic drugs for Parkinson's disease (dopamine D_2-receptor agonists)].

(4) Others: antidiarrheals such as opioid-receptor agonists (e.g., loperamide), antineoplastic agents (e.g., hydroxyurea), antiasthmatics such as phosphodiesterase IV inhibitors (e.g., rolipram), histamine, pilocarpine, protoveratrine, levodopa, theophylline, hydroxycarbamide, thiotepa, carboplatine, epirubicin, etc.

Please replace the first full paragraph on page 15 as follows:

The emetic drugs include a combination of the above-mentioned agents (preferably, a combination of two or three agents). The compounds represented by General Formula (I) ~~according to the present invention~~ are effective for preventing vomiting caused by μ-opioid agonists among the above-mentioned agents, and are preferably used for preventing vomiting due to opioid analgesics such as morphine, its derivatives, and its salts, or due to antidiarrheals such as opioid-receptor agonists (e.g., loperamide), specifically due to opioid analgesics such as morphine, its derivatives, and its salts.

Please replace the first full paragraph on page 16 as follows:

The therapeutic or prophylactic agents for preventing nausea and vomiting ~~according to the present invention~~ are mixed with pharmacologically acceptable carriers and are administered orally or parenterally as, for example, solid pharmaceutical preparations such as powders, granules, tablets, and capsules; liquid pharmaceutical preparations such as syrups, emulsions, and injections

(hypodermic injections, intravenous injections, intramuscular injections, and drip infusions); sustained-release preparations such as sublingual tablets, buccals, troches, and microcapsules; intraoral fast-dissolving preparations, or suppositories. These dosage forms are prepared by known pharmaceutical preparation technologies.

Please replace the paragraph spanning pages 18 and 19 as follows:

The compounds ~~according to the present invention~~ can be used with the above-mentioned emetic agents (1) in the forms of pharmaceutical preparations (pharmaceutical compositions) containing a compound represented by General Formula (I) and an emetic agent, or (2) by preparing the compound represented by General Formula (I) and the emetic drug and by separately or simultaneously prescribing the compound represented by General Formula (I) and the emetic drug. Doses of the compounds ~~of the present invention~~ are appropriately determined in accordance with symptom severity, subject age, weight, and route of administration. An effective daily dose for an adult ranges from 0.1 μg to 100 g, preferably from 1 μg to 1 g, and more preferably from 10 μg to 100 mg, and is administered in one dose or split into two or more separate doses in a day.

Please replace the paragraph spanning pages 19 and 20 as follows:

When the compounds ~~of the present invention~~ are used as therapeutic or prophylactic agents for preventing nausea and vomiting, the following agents may be simultaneously used with the compounds of the present invention for reducing vomiting, preventing vomiting, and increasing anti-emetic efficacy: autonomic blocking agents; anti-dopamine agents; serotonin antagonists [for example, ondansetron (Zofran) and its sustained-release preparation (Zofran Zydis), granisetron (Kytril), azasetron (Serotone), ramosetron (Nasea), metoclopramide (Primperan) and its sustained-release preparation (Pramidin), tropisetron (Novoban), mosapride (Gasmotin), dolasetron (Anemet), palonosetron (RS-42358-197), itasetron (U-98079A), indisetron (N-3389), KAE-393, R-zacopride

(SL-920241), lerisetron (F-0930-RS), E-3620, and Ro-93777]; histamine antagonists; parasympatholytic agents; anti-emetic agents (for example, metopimazine, trimethobenzamide, benzquinamine hydrochloride, and diphenidol hydrochloride); glucosteroids [for example, cortisone acetate (Cortone), hydrocortisone (Cortril, Hydrocortone) and its sodium phosphate salt (hydrocortisone soluble), dexamethazone (Corson, Decaderon, Decaderon S), its acetate salt (Decadron A injection aqueous suspension, etc.), its sodium phosphate salt (Decadron, Decadron injection solution, Decadron S), and its sodium sulfate salt (Dexa-Scheroson injection solution, Dexa-Scheroson injection solution B), betamethasone (Rinderon, Betonelan), its sodium phosphate salt (Rinderon), and its acetate salt (Rinderon suspension), prednisolone (Predonine, prednisolone tablets, etc.), its acetate salt (Predonine soluble), its sodium phosphate salt (Dojilon injection), its butyl acetate salt (Codelcortone), and its sodium succinate salt (Predonine soluble), methylpredonine (Medrol), its acetate salt (Depo-Medrol), and its sodium succinate salt (Sol-Medrol), triamcinolone acetate (Kenacort), and other adrenocortical steroids such as steroids having glucocorticoid activities, and their salts]; psycholeptics such as chlorpromazine; and tranquilizers. In particular, serotonin antagonists such as ondansetron; and glucosteroids such as dexamethasone, its acetate salt, its sodium phosphate salt, and its sodium sulfate salt are preferably used together.

Please replace the first full paragraph on page 20 as follows:

The compounds ~~of the present invention~~ can be used as pharmaceutical preparations (pharmaceutical compositions) containing a compound represented by General Formula (I) and a concomitant drug such as the above-mentioned serotonin antagonists.

Please replace the paragraph spanning pages 20 and 21 as follows:

The compounds ~~of the present invention~~ can be used in the forms of pharmaceutical preparations (pharmaceutical compositions) (1) containing a compound represented by General

Formula (I), an emetic agent, and a serotonin antagonist, (2) containing a compound represented by General Formula (I), an emetic drug, and glucosteroid, or (3) containing a compound represented by General Formula (I), an emetic drug, a serotonin antagonist, and glucosteroid.

Please replace the paragraph spanning pages 21 and 22 as follows:

Medicines ~~according to the present invention~~ may be simultaneously administered with the emetic drugs. An emetic drug is administered in advance and then a compound represented by General Formula (I) may be administered before or after the onset of vomiting, or the compound represented by General Formula (I) is administered in advance and then the emetic drug may be administered. When there is a time interval between the administrations of the compound and the emetic drug, the time interval is determined in accordance with the active substance, the dosage form, and the administration method. For example, when an emetic drug is administered in advance, a compound represented by General Formula (I) is administered between one minute and three days after the administration of the emetic drug, preferably between ten minutes and one day, more preferably between fifteen minutes and one hour after the administration of the emetic drug. When a compound represented by General Formula (I) is administered in advance, an emetic drug is administered between one minute and one day after the administration of the compound represented by General Formula (I), preferably between ten minutes and six hours, more preferably between fifteen minutes and one hour after the administration of the compound represented by General Formula (I). When a medicine according to the present invention is administered with a serotonin antagonist or glucosteroid, the serotonin antagonist and the glucosteroid may be simultaneously administered with the compound represented by General Formula (I) or may be administered at different times. When these drugs are administered at different times, for example, when an emetic drug is administered in advance, the drugs are administered between one minute and three days after

the administration of the emetic drug, preferably between ten minutes and one day, more preferably between fifteen minutes and one hour after the administration of the emetic drug.

Please replace the the first full paragraph on page 22 as follows:

EXAMPLES

The ~~present invention~~ disclosure will now be explained in detail with reference to COMPARATIVE EXAMPLES and EXAMPLES hereinafter.